HYDROACRIDINES AND RELATED COMPOUNDS

VIII.* N-OXIDES OF OXAHYDROACRIDINES AND SOME OF THEIR DERIVATIVES

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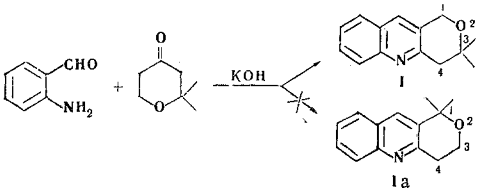
3,3-Dimethyl-2-oxa-1,2,3,4-tetrahydroacridine and its N-oxide and 3,3,6,6-tetramethyl-2,7-dioxa-sym-octahydroacridine N-oxide were synthesized. On heating with acetic anhydride, the N-oxides form, respectively, acetates of 3,3-dimethyl-2-oxa-1,2,3,4-tetrahydro-4-acridinol and 3,3,6,6-tetramethyl-2,7-dioxa-sym-octahydro-4-acridinol. Hydrolysis of the acetates gives the alcohols themselves. Oxidation of 3,3,6,6-tetramethyl-2,7-dioxa-sym-octahydro-4-acridinol acetate gives the corresponding N-oxide. Oxidation of 3,3,6,6-tetramethyl-2,7-dioxa-sym-octahydro-4-acridinol with manganese dioxide gives 3,3,6,6-tetramethyl-2,7-dioxa-sym-octahydro-4-acridinone.

In [1,2] it was reported that various substituents are readily introduced into the 4 position of the octahydroacridine ring on the basis of the reaction of sym-octahydroacridine N-oxide with acetic anhydride. It seemed of interest to study the occurrence of this reaction in a number of oxahydroacridines. With this intent, we synthesized N-oxides III and IV and studied their behavior with respect to acetic anhydride.

We synthesized the base (I) necessary for the preparation of oxide III by means of the Friedlaender reaction starting from o-aminobenzaldehyde and α,α-dimethyltetrahydro-γ-pyrone. The Pfitzinger method gives poorer results, and it is possible that self-condensation of the ketone occurs under these rather severe conditions (refluxing for 8 h in 30% KOH):



Base I is obtained in almost quantitative yield. The possible alternative structure (Ia) is not detected by NMR spectroscopy: both methylene groups are in the 1 and 4 positions and not in the 3 and 4 positions. In addition to other signals (protons of the gem-methyl groups and aromatic protons), the NMR spectrum contains two singlets at 2.5 ppm (C_4 protons) and 4.8 ppm (C_1 protons).

Oxidation of bases I and II with hydrogen peroxide in acetic acid gives N-oxides III and IV.

The IR spectra of the N-oxides contain intense absorption bands at 1335 cm^{-1}, which are absent in the spectra of the starting bases and can be assigned to the valence vibrations of the N-oxide group. In order to additionally confirm the structure of oxide IV, we reduced it with iron in acetic acid. Base II was obtained.

Rearrangement occurs when oxides III and IV are refluxed with acetic anhydride, and acetates V and VI are formed. In connection with the fact that acetate V could not be purified, it was characterized as the

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*See [9] for communication VII.

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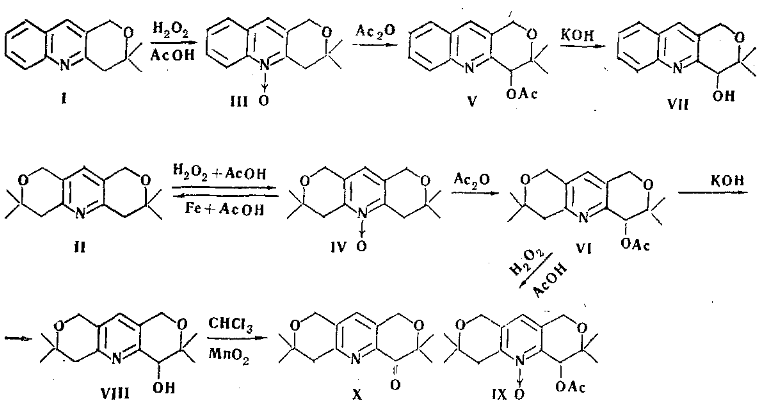

picrate and hydrochloride. The IR spectrum of amino ester VI contains absorption bands at 1745 and 1245 cm^{-1} caused by the vibration of the ester grouping.

Acetates V and VI are harder to hydrolyze than the acetates of sym-octahydro-4-acridinols that do not have substituents in the 3 position; alcohols VII and VIII are obtained. In place of the absorption bands characteristic for the ester grouping, absorption bands at 3470-3480 cm^{-1}, which are caused by the presence of a hydroxyl group involved in intramolecular hydrogen bonding, appear in the IR spectra of VII and VIII.

In connection with the fact that the hydrolysis of amino esters V and VI proceeds with greater difficulty than in the case of acetates of sym-octahydro-4-acridinols, it seemed of interest to study the behavior of them with respect to the action of hydrogen peroxide in acetic acid. In [3] it was demonstrated that hydrolysis occurs simultaneously in the oxidation of the unsubstituted acetate of sym-octahydro-4-acridinol to form sym-octahydro-4-acridinol N-oxide. In the case of oxidation of acetate VI we found that hydrolysis does not occur, and the corresponding N-oxide (IX) is obtained. There are absorption bands characteristic for the N-oxide (1310 cm^{-1}) and ester (1730 and 1250 cm^{-1}) groups in the IR spectrum of this compound.

The oxidation of amino alcohol VIII by active manganese dioxide in chloroform gives ketone X. The IR spectrum of this compound contains an absorption band characteristic for a conjugated carbonyl group at 1710 cm^{-1}. Amino ketone X forms an oxime; such oximes, which are analogs of 2-formylpyridine oxime, are of interest as phosphorylated cholinesterase reactivators [4].

EXPERIMENTAL

The IR spectra of CCl_4 (I, VI-VIII, and X) and $CHCl_3$ (III, IV, and IX) solutions were recorded with a UR-20 spectrophotometer with NaCl and LiF prisms. The NMR spectrum of a CCl_4 solution was recorded with a ZKR-60 spectrometer. Activity-II aluminum oxide was used for the chromatography; the spots were developed with iodine vapors. The picrates were obtained by mixing alcohol solutions of the compounds and picric acid. The hydrochlorides were obtained by bubbling dry hydrogen chloride through ether (I, V, VI, VIII), benzene (X), or alcohol (IV, with subsequent evaporation) solutions of the compounds.

3,3-Dimethyl-2-oxa-1,2,3,4-tetrahydroacridine (I). A mixture of 2.55 g (0.021 mole) of o-aminobenzaldehyde [5] and 2.55 g (0.019 mole) of α,α-dimethyltetrahydro-γ-pyrone [6] in 10 ml of 0.01% alcoholic potassium hydroxide was refluxed for 1 h, 45 ml of water was added, and the oil that separated was extracted with three 15-ml portions of chloroform. The extract was passed through a column filled with aluminum oxide with elution by chloroform. The eluate was evaporated to give 4 g (94%) of yellowish needles with a quinoline odor that melted at 56-57° (from petroleum ether) and were soluble in the usual organic solvents. R_f 0.71 ($CHCl_3$). Found %: C 78.57; H 7.16; N 6.60. $C_{14}H_{15}NO$. Calculated %: C 78.47; H 7.04; N 6.57. NMR spectrum: 1.3 ppm (singlet of two gem-methyl groups), 2.5 ppm (singlet of C_4 protons), 4.8 ppm (singlet of C_1 protons), 7.5 ppm (several aromatic proton peaks). The picrate was obtained as lemon-yellow rods with mp 203-204° (from alcohol). Found %: N 12.70. $C_{14}H_{15}NO \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 12.67. The hydrochloride was obtained as yellowish rods with mp 183-184° (from benzene) that were quite soluble in water. Found %: N 5.68. $C_{14}H_{15}NO \cdot HCl$. Calculated %: N 5.61.

3,3-Dimethyl-2-oxa-1,2,3,4-tetrahydroacridine N-Oxide (III). A mixture of 3.5 g (0.016 mole) of base I, 4 ml of 30% hydrogen peroxide, and 12 ml of 98% acetic acid was heated for 5 h at 75°; 2 ml of H_2O_2 was added, and the mixture was heated for another 2 h. The cooled solution was made alkaline with potassium carbonate solution; 2.9 g (77%) of crystals of oxide III precipitated. The yellow rods melted at 90-91° (from petroleum ether) and were quite soluble in polar solvents and slightly soluble in nonpolar solvents. R_f 0.2 [$CHCl_3$–acetone (10 : 1)]. Found %: C 72.56; H 6.59; N 6.26. $C_{14}H_{15}NO_2$. Calculated %: C 73.56; H 6.55; N 6.11. The picrate was obtained as yellow rods with mp 131-133° (from alcohol). Found %: N 12.29. $C_{14}H_{15}NO_2 \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 12.27.

3,3,6,6-Tetramethyl-2,7-dioxa-sym-octahydroacridine N-Oxide (IV). This was similarly obtained from base II [7] in 82% yield as white rhombi with mp 216-217° (from acetone) that were quite soluble in polar solvents and slightly soluble in ether. R_f 0.76 [$CHCl_3$–acetone (6 : 1)]. Found %: C 68.50; H 8.24; N 5.32. $C_{15}H_{21}NO_3$. Calculated %: C 68.44; H 8.04; N 5.32. The picrate was obtained as yellow rods with mp 150-151° [from aqueous methanol (1 : 1)]. Found %: N 11.53. $C_{15}H_{21}NO_3 \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 11.38. The hydrochloride was obtained as white needles with mp 185-185.5° (from dibutyl ether) that were quite soluble in hot water. Found %: Cl 11.84. $C_{15}H_{21}NO_3 \cdot HCl$. Calculated %: Cl 11.72.

Reduction of Oxide IV. A mixture of 1.4 g (0.005 mole) of oxide IV, 1 g of reduced iron, and 15 ml of dilute (1 : 2) acetic acid was refluxed for 2 h, filtered, made alkaline with saturated sodium carbonate solution, and extracted with chloroform to give 1.2 g (92%) of white rhombi of II with mp 116-117° (from water). This product did not depress the melting point of an authentic sample of II (116-117°). The R_f values for both compounds were 0.45 ($CHCl_3$).

3,3,6,6-Tetramethyl-2,7-dioxa-sym-octahydro-4-acridinol Acetate (VI). A mixture of 10 g (0.038 mole) of oxide IV and 38 ml of acetic anhydride was refluxed for 2 h, cooled, and made alkaline with saturated potassium carbonate to precipitate 11.2 g (76%) of white rods of acetate VI with mp 92-93° (from petroleum ether) that were quite soluble in the usual organic solvents. R_f 0.52 [$CHCl_3$–acetone (1 : 1)]. Found %: C 67.08; H 7.69; N 4.60. $C_{17}H_{23}NO_4$. Calculated %: C 66.88; H 7.54; N 4.59. The picrate was obtained as lemon-yellow plates with mp 187-188° [from n-propanol–benzene (1 : 1)]. Found %: N 10.42. $C_{17}H_{23}NO_4 \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 10.48. The hydrochloride was obtained as white needles with mp 203-204° (from dioxane) that were quite soluble in water. Found %: Cl 9.39. $C_{17}H_{23}NO_4 \cdot HCl \cdot 2H_2O$. Calculated %: Cl 9.39. When 0.3325 g of the salt was heated in vacuo it lost 0.0312 g of water (calculated 0.0317 g of H_2O). The anhydrous hydrochloride melted at 211-214°.

3,3-Dimethyl-2-oxa-1,2,3,4-tetrahydro-4-acridinol Acetate (V). This was similarly obtained in 93% yield from oxide III. The liquid could not be vacuum distilled. R_f 0.48 [$CHCl_3$–acetone (10 : 1)]. The picrate was obtained as yellow plates with mp 184-185° (from alcohol). Found %: N 11.48. $C_{16}H_{17}NO_3$ $C_6H_3(NO_2)_3OH$. Calculated %: N 11.19. The hydrochloride was obtained in 78% yield as sand-colored rods with mp 168-169° (from ethyl acetate) that were soluble in water. Found %: N 4.80. $C_{16}H_{17}NO_3 \cdot HCl$. Calculated %: N 4.77.

3,3,6,6-Tetramethyl-2,7-dioxa-sym-octahydro-4-acridinol Acetate N-Oxide (IX). This was obtained in the same way as oximes III and IV in 68% yield as white rods with mp 175-176° [benzene–cyclohexane (1 : 1)] that were only slightly soluble in nonpolar solvents. R_f 0.32 [$CHCl_3$–acetone (6 : 1)]. Found %: C 63.56; H 7.47; N 4.38. $C_{17}H_{23}NO_5$. Calculated %: C 63.56; H 7.21; N 4.36.

3,3-Dimethyl-2-oxa-1,2,3,4-tetrahydro-4-acridinol (VII). A mixture of 3.2 g (0.011 mole) of acetate V and 17 ml of 20% alcoholic potassium hydroxide was refluxed for 4 h, filtered, diluted with water, and extracted with three 15-ml portions of chloroform. Trituration with petroleum ether gave 1.3 g (50%) of yellowish rods with mp 93-94° (from petroleum ether) that were only slightly soluble in nonpolar solvents. R_f 0.24 ($CHCl_3$). Found %: C 72.91; H 6.27; N 6.70. $C_{14}H_{15}NO_2$. Calculated %: C 73.56; H 6.55; N 6.11. The picrate was obtained as lemon-yellow plates with mp 177-179° (from alcohol). Found %: N 11.65. $C_{14}H_{15}NO_2 \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 12.22.

3,3,6,6-Tetramethyl-2,7-dioxa-sym-octahydro-4-acridinol (VIII). This was similarly obtained from acetate VI in 92% yield as white rods with mp 91-92° (from petroleum ether) that were quite soluble in polar solvents. R_f 0.21 [$CHCl_3$–acetone (3 : 2)]. Found %: C 68.50; H 8.49; N 5.36. $C_{15}H_{21}NO_3$. Calculated %: C 68.44; H 8.04; N 5.32. The picrate was obtained as yellow plates with mp 173-174° (from methanol). Found %: N 11.14. $C_{15}H_{21}NO_3 \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 11.38. The hydrochloride was obtained as white needles with mp 232-234° [ethyl acetate–$CHCl_3$ (10 : 1)] that were quite soluble in water. Found %: Cl 11.75. $C_{15}H_{21}NO_3 \cdot HCl$. Calculated %: Cl 11.85.

3,3,6,6-Tetramethyl-2,7-dioxa-sym-octahydro-4-acridinone (X). A mixture of 2.7 g (0.01 mole) of alcohol VIII, 4 g of active manganese dioxide [8], and 10 ml of $CHCl_3$ was stirred for 5 h at room temperature; 2 g of MnO_2 was added, and the mixture was stirred for another 3 h. The manganese dioxide was removed by filtration and washed with $CHCl_3$. The solvent was evaporated to give 2.4 g (90%) of crystalline ketone X as gray plates with mp 156-157° [from petroleum ether–$CHCl_3$ (11 : 1)] that were soluble in the usual organic solvents. R_f 0.68 [benzene–methanol (5 : 1)]. Found %: C 68.48; H 7.27; N 5.25. $C_{15}H_{19}NO_3$. Calculated %: C 68.96; H 7.28; N 5.36. The IR spectrum contained a band at 1710 cm^{-1} (carbonyl group). The picrate was obtained as yellow rods with mp 161-162° (dec., from alcohol). Found %: N 11.13. $C_{15}H_{19}NO_3 \cdot C_6H_3(NO_2)_3OH$. Calculated %: N 11.15. The hydrochloride was obtained as white rhombic plates with mp 203-204° (from dioxane) that were quite soluble in water. Found %: N 5.13. $C_{15}H_{19}NO_3 \cdot HCl$. Calculated %: N 4.70. The oxime was obtained by refluxing 2.05 g (0.0078 mole) of ketone X and 0.8 g (0.011 mole) of hydroxylamine hydrochloride in a mixture of 12 ml of methanol and 2.5 ml of water for 1.5 h. The methanol was evaporated, and the residue was made alkaline with 1% KOH to precipitate the oxime as white rhombi with mp 150-152° (from C_6H_6). Found: N 10.08%. $C_{15}H_{19}N_2O_3$. Calculated: N 10.14%. The hydrochloride was obtained as white needles with mp 194-195° (from methanol). Found %: N 9.60. $C_{15}H_{19}N_2O_3 \cdot HCl$. Calculated %: N 8.97.

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